UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,909	02/02/2001	Mark Roberts	M0975/7006 (JRV)	9660

7590 07/08/2003

John R. Van Amsterdam
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	12

DATE MAILED: 07/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/775,909	Roberts et al
Examiner	**Art Unit**
Patricia A. Duffy	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 7, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *37, 39, and 41-55* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *37, 39, 41-46, and 55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *37, 39, and 41-55* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The amendment filed 5-5-03 has been entered into the record. Claims 37, 39, and 41-54 are pending. Claims 47-54 are withdrawn from consideration as drawn to non-elected inventions

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections/Objections Withdrawn

Priority

3. The examiner acknowledges the update of the priority information in the first line of the specification. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

4. The corrected or substitute drawings were received on 5-7-03. These drawings are acceptable.

Specification

5. The objection to the title is withdrawn in view of Applicant's amendment.

6. The objection to the application as informal in the arrangement of the specification is withdrawn based on Applicant's amendments.

7. The rejection of claims 37, 38, 40, 42-44 under 35 U.S.C. 102(b) as being anticipated by Capiau et al (EP 352250, published 1-24-90) is withdrawn based on Applicant's amendments to the claims.

Rejections/Objections Maintained

Oath/Declaration

8. The oath or declaration still defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The declaration filed 5-3-03 is still defective because it has not been executed in accordance with 37 CFR 1.67(a)(1).

9. This application does still not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required in response to this office action.

10. Claims 37, 39, 41-44, 46 and new claim 55 stand rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Nencioni et al (Acta. Med. Rom. 29:78-83, 1991) or Podda et al (J. Exp. Med. 172:861-868, 1990) in view of Capiau et al (EP 352250, published 1-24-90), Tamura et al (U.S. Patent No. 5,182,109) and Honda et al (Japanese Application #3-135923) for reasons made of record for claims 37-44 and 46 in Paper No. 6, mailed 12-31-02.

11. The rejection of claim 45 under 35 U.S.C. 103(a) as being unpatentable over Nencioni et al (Acta. Med. Rom. 29:78-83, 1991) or Podda et al (J. Exp. Med. 172:861-868, 1990); Capiau et al (EP 352250, published 1-24-90), Tamura et al (U.S. Patent No. 5,182,109) and Honda et al (Japanese Application #3-135923) as applied to claims 37-44 and 46 above and further in view of Halpern et al (Infection and Immunity 58(4):1004-1009, 1990) is maintained for reasons made of record in Paper No. 6, mailed 12-31-02.

Inasmuch as, the rejections were addressed together they will be rebutted together. Applicant's arguments have been carefully considered but are not persuasive. Applicant argues that it would not have bee obvious to combine either of the primary references with the secondary references. Applicant argues that their must be some suggestion or motivation in the references or knowledge generally available to one of ordinary skill in the art to modify or combine the references. Applicant asserts that there was no motivation to combine the references. This is not persuasive. Honda et al explicitly teach that nasal inoculation of pertussis toxin and a vaccine antigen produces an immune response which is greater than subcutaneous administration, Tamura et al teaches that nasal administration has the benefit of inducing an IgA response and Capiau et al teach oral or intranasal administration of double mutant pertussis toxins in combination with other antigens such as FHA and such as filamentous hemagglutinin (FHA), tetanus toxoid and/or diphtheria toxoid or any other protective antigen of *Bordatella pertussis* for the protection

from disease. The combined teachings of the prior art suggest to one of skill in the art that vaccines comprised of bacterial toxins such as pertussis toxin, can be administered intranasally in the form of nasal drops or nasal sprays in order to produce an greater immune response. Applicant asserts hindsight reconstruction. In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Honda provides more than sufficient motivation in combination with Capiau et al that teaches administration of non-toxic mutants. Applicant arguments ignore the direct teachings of Capiau et al and Honda et al. There is explicit unambiguous motivation to combine the references. Applicants argue that mucosal administration was not a preferred route and the art teaches that administration is almost always carried out by subcutaneous administration. This is not persuasive, Honda et al specifically teach that nasal administration was superior to subcutaneous administration. As such, there is unambiguous indication in the art that nasal administration was SUPERIOR to subcutaneous for pertussis toxin. As such, Applicant's allegation of the state of the art is erroneous. Clearly one

skilled in this art at the time that the invention was made, that for pertussis toxin in combination with antigens, nasal vaccination was SUPERIOR. Applicants argue that the means of administration recited by Capiau et al were "throwaway" and provides no advantages for such. This is not persuasive, Applicants admit that Capiau et al teaches oral and intranasal administration and the advantages are provided by Honda et al. Applicants arguments are not persuasive, because it addresses the references individually and not the rejection as combined. Applicants argue that Tamura teaches away from the use of pertussis toxin as an adjuvant. This is not persuasive, issued patents are presumed valid (35 U.S.C. 282) and Applicant can not attack the combination of references by impugning the validity of an issued US Patent. This is also not persuasive because the MPEP 2123 states:" A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 10 USPQ2d 1843 (Fed. Cir. 1989)." Moreover, " Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)." and ""The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are

concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968))." This is not also persuasive, the references provide clear motivation to combine the double mutant pertussis toxin with the other claimed antigens and the references does not teach that the combination was ineffective to produce an immune response. Applicants argue that Honda et al teach away by teaching only the use of the beta subunit and there is no evidence that one would expect similar adjuvant activity for the S1 subunit or double mutant thereof. This is not persuasive, Applicant admits at page 6, lines 2-4 that "Pertussis toxin (PTX) has been reported to have adjuvant properties,....". This is also not persuasive because the art of record indicates that mere adenylate cyclase activity of a molecule does not confer adjuvant activity to a molecule indicating "a role for cholera and pertussis toxin which is independent of enhancement of adenylate cyclase activity in the regulation of the immune response" and adjuvant activity is independent of the enzymatic activity. The art of record teaches that despite loss of enzymatic activity the detoxified mutants of pertussis toxin retain all the other functional characteristics of the wild type pertussis toxin. The references as combined support the use of mutant pertussis toxin as an immunogen and as an adjuvant because the native protein was viewed to evidence adjuvant activity and that activity was demonstrated to be independent of enzymatic activity of the toxin (Honda et al). Therefore, the mutant toxin

would necessarily evidence adjuvant activity and one of skill in the art would recognize this because it had the B subunit in the toxin. Further, the pertussis toxin administered by the art as combined is the double mutant pertussis toxin PT-9K/129G which comprises both the B and S1 subunits and therefore the PT-9K/129G as cited by the examiner would be recognized by the art as possessing adjuvant activity. Applicant's attention is drawn to Podda et al that teach that vaccination caused in increase in response to both the S1 and B oligomer (see abstract). Podda et al teach that the non-toxic double mutant was made by modification of two codons in the gene of PT and obtained a *Bordatella pertussis* strain the secretes a pertussis toxin molecule that is naturally devoid of toxicity. The secreted PT-9K/129G toxin of the prior art comprises both the genetically detoxified mutant S1 subunit and the B oligomer. The presence of the B oligomer is specifically indicated as present by Podda et al (see abstract and page 862, column 2, "Antigens". Podda et al teach that the PT-9K/129G retains the ability to bind the receptors on eukaryotic cells. Honda teach that the B subunit participates in cell adsorption and enhances the immune response. The claimed composition is not limited to the administration of the S1 subunit alone, the claim merely requires an effective adjuvant amount of a non-toxic double mutant form of pertussis toxin comprising an S1 subunit with modifications at positions 9K/129G. This is not incompatible with the teachings of Hoda et al because Hoda et al teach that the B subunit provides for the advantage and one would not necessarily want the S1 because it provided for toxicity,

however Podda et al or Nencioni et al teach that the toxin comprising the detoxified S1 subunit provides for effective vaccination without the toxic effects. As such, the art as combined does not teach away. Further, Podda et al teach the use of 15 ug/dose of the double mutant pertussis toxin and this amount is considered as an adjuvant amount according to the specification page 11 of 1-100 ug/dose. The references clearly teach that the mutant PT-9K/129G enhances the immune response through mitogenic character and therefore would function as an adjuvant as reported by the art and acknowledged by Applicant on page 6 of the specification. Applicants argue that the double mutant provided for unexpectedly higher responses than the native PT toxin. This is not persuasive, Podda et al teach that 15 ug of mutant PT-9K/129G induces a humoral response higher than that obtained using 50 or 25 ug of detoxified PT (see page 867, column 1, first full paragraph). The increase in the response as compared to unaltered PT and the increase is not "unexpected" to the art. Further, the description in the specification fails to indicate the actual amounts of PT and mutant PT-9K/129G administered nasally per dose. As such, no direct comparison of the two administrations can be readily ascertained in the absence of such a comparison. Even if the identical amounts were administered nasally, the showing of unexpected results are not commensurate in scope with the claims. To warrant the allowance of generic claims, the showing of unobviousness must include enough examples to be reasonably representative of the genus. Further, Applicants appear to argue that the S1 subunit alone is responsible for

adjuvant activity. There is no showing or evidence on the record that the S1 subunit alone has any adjuvant activity. Applicants argue that the Examples of Roberts et al are opposite of what would have been expected since the mutations at positions 9 and 129 recited in the claims are designed to destroy the toxic activity of the toxin and would not be expected to have the ability to induce an immune response and particularly an immune response that recognizes the native form of the toxin. This is also not persuasive, Nencioni et al teach that while the double amino acid substitutions did not show any of the toxic properties of pertussis toxin such as lymphocytosis, histamine sensitivity, potentiation of anaphylaxis, hyperinsulinaemia and acute toxicity, that the double mutant MAINTAINED all the physicochemical and antigenic properties of the native toxin confirming that the mutations introduced had not altered the immunological properties of the molecule (page 80, third-fourth full paragraph). Further, Nencioni et al teach that one injection of the PT-9K/129G vaccine was able to induce high titers of antibodies specific for PT with strong neutralizing activity (page 82, second full paragraph). As such, Applicants allegation that one would not expect that the mutant toxin to induce an immune response that recognizes the native form to the toxin is erroneous. The findings of Roberts are not opposite to the art and are completely expected.

The rejections are maintained

Status of Claims

12. All claims stand rejected.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
July 5, 2003

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600